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EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/674,716

Applicant(s)

BONNEFOY ET AL.

Examiner

Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12 and 18-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12 and 18-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 November 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/27/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/27/04 has been entered.
2. Claims 1-10, 12, and 18-22 are pending and are being acted upon in this Office Action.
3. Claims 2, 4-5 and 7 are objected to because "A" should have been "The" for said dependent claims.
4. Claim 7 is objected to because the specification fails to provide antecedent for "the framework of the light chain included the amino acid residues from the murine antibody **at position 64** by the Kabat numbering system".
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1-10, 12, and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for:

(1) A monoclonal antibody that binds specifically to the CD23 (FCεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11, CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13 for diagnostic purpose;

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(2) the monoclonal antibody mentioned above which binds to CD23 with an affinity constant equal to or greater than 1×10^9 Ka Mol⁻¹;

(3) A humanized antibody or chimeric antibody that binds specifically to the CD23 (FcεRII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13;

(4) The humanized antibody wherein the framework of the heavy chain retains the mouse heavy chain amino acid residues at position 49, 66, 76, 77 and 94 according to the Kabat numbering system and the framework of the light chain retains the mouse light chain amino acid residue at position 64 according to the Kabat numbering system;

(5) An antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising the amino acid sequences encoded by the nucleic acid sequences according to SEQ ID NO: 1 *and* SEQ ID NO: 2;

(6) An antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising the amino acid sequences encoded by the nucleic acid sequences according to SEQ ID NO: 17 *and* SEQ ID NO: 8;

(7) A pharmaceutical formulation comprising the antibody as set forth in claim 1 and a pharmaceutically acceptable excipient.

(8) A pharmaceutical formulation comprising the antibody as defined in claim 1 in combination with an anti-inflammatory agent and a pharmaceutically acceptable excipient.

(9) A method of making any antibody mentioned above for diagnostic purpose and for screening for antibody which competitively inhibits the binding of any antibody mentioned above, and (10) a method of treating rheumatoid arthritis comprising administering the specific antibody mentioned above, **does not** reasonably provide enablement for: (1) any antibody which comprises the amino acid sequence as set forth in claim 1 without the heavy and light chain framework regions as set forth in claims 1-2, (2) any antibody which competitively inhibits the binding of the any antibody which comprises the amino acid sequence as set forth in claim 1

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without the heavy and light chain framework regions to the CD23 type II molecule expressed on haematopoietic cells, (3) any antibody which comprises the amino acid sequence as set forth in claim 1 in which the framework of the heavy chain "includes" all amino acid residues from the murine antibody at any positions 49, 66, 76, 77 and 94 by the Kabat numbering system, (4) any antibody which comprises the amino acid sequence as set forth in claim 1 in which the framework of the light chain "includes" all amino acid residues from the murine antibody at any position 64 by the Kabat numbering system, (5) any pharmaceutical formulation comprising any antibody which comprises the amino acid sequence as set forth in claim 1 without the heavy and light chain framework regions as set forth in claims 1-2 and a pharmaceutically acceptable excipient, (6) any pharmaceutical formulation comprising any antibody which comprises the amino acid sequence as set forth in claim 1 without the heavy and light chain framework regions as set forth in claims 1-2 in combination with any immunomodulatory or anti-inflammatory agent and a pharmaceutically acceptable excipient, (7) any antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising *one* of the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 1 and 2, (8) any antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising *one* of the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 17 and 18, (9) any antibody which comprises the amino acid sequence as set forth in claim 1 wherein the constant region contains Ala at position 235 and Ala at position 237 by the Kabat numbering system, (10) a method of treating or prophylaxis of any disorder such as the ones recited in claim 12, (11) any antibody which competitively inhibits binding of any antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising *one* of the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 1 and 2, (12) any antibody which competitively inhibits binding of any antibody which binds to the CD23 (FCRII) type II molecule expressed on haematopoietic cells comprising *one* of the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 17 and 18 for treating or prophylaxis of any disorder such as lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema, GVH, COPA, insulinitis, bronchitis (particularly chronic bronchitis), diabetes (particularly Type 1 diabetes) and B-cell malignancies. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one monoclonal antibody that binds to CD23 (FC ϵ RII), a type II molecule expressed on haematopoietic cells wherein the antibody comprises the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 1 and SEQ ID NO: 2 for detection of disorder such as the ones recited in claim 12. The specification discloses only one humanized antibody that binds to CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 17 and SEQ ID NO: 18. The specification further discloses the monoclonal CD23 antibody that binds to the CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13. The specification further discloses that the said monoclonal antibody has affinity constant (K_a) approximately 9×10^{10} /mol for screening for competitive inhibitor.

Claims 3, 21 and 22 encompass any antibody that competitively inhibits the binding of any antibody that comprises the CDRs having the amino acid sequences as recited in claim 1. Claim 1-2, 4-7, 8-9, 10, 18 and 19 encompass any antibody having any heavy and light chain framework, and any effector functions for treating any disorders such as the ones recited in claim 12.

The specification does not teach how to make all antibody as set forth in claims 1-10, 12, and 18-22 having any heavy and light chain framework, any murine residues at position 49, 66, 76, 77 and 94 in the heavy chain, any murine residues at position 64 in the light chain without the amino acid sequence, much less about how to treat or prophylaxis of any disorder such as lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema, GVH, COPA, insulinitis, bronchitis (particularly chronic bronchitis), diabetes (particularly Type 1 diabetes) and B-cell malignancies.

Ward et al teach the use of rodent monoclonal antibodies in therapy is limited by the immunogenicity of rodent of these proteins in xenogeneic hosts (See page 79, col. 1, in particular) and short half-life (page 87, col. 1, in particular). Ward et al teach chimeric antibodies still contain rodent framework which result in the generation of anti-mouse variable domain response while humanized antibodies still contain rodent hypervariable regions grafted to human framework sequences (See page 79, col. 2, pars 1-2, in particular). Ward et al further teach changing some of the amino acids in the effector domain or the Fc region of the antibody molecules can lead to either increase or decrease the targeted effector function, increase or decrease its half-life, and/or abolish its complement mediated lysis (See entire document). Given the chronic nature of the disorders such as arthritis, lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema which require long term treatment using the antibody, it is not clear the reliance of antibody such as polyclonal or antibody having any heavy and light chain framework and effector function is effective for treating all chronic autoimmune diseases in the absence of in vivo working example.

Mavromatis et al teach agent such as monoclonal antibodies when use individually are unlikely to lead to a significant prolongation of patient survival in the treatment of chronic lymphocytic leukemia (See page 1879, col. 2, in particular).

Further, autoimmune diseases such as the ones recited in claim 12 can be species- and model-dependent. It is not clear that the reliance on in vitro binding assays accurately reflects the relative efficacy of using any undisclosed antibody for the claimed method.

Van Noort *et al* teach that induction of EAE with MBP does not result in the development of relapse and the clinical course may be different than that after treatment with

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other antigen such as SCH and PLP (See page 170, in particular). There is no showing of treating any animal with the claimed antibody alone or in combination with any immunomodulatory or anti-inflammatory agent in the specification as filed and whether the claimed pharmaceutical composition and method are effective for treating or preventing a wide range of diseases from autoimmune disease to B cell malignancy.

It is also not clear the use of antibody that binds to CD23 (FcRII) type II molecule expressed on haematopoietic cells is effective to treat disorder such as the ones recited in claim 12 which associated with an increase in soluble CD23 since the soluble CD23 are the consequence of membrane bound CD23(FcRII) type) being release from membrane bound CD23. With regard to autoimmune disease, Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document, Science 300: 1862-65, 2003).

With regard to B cell malignancies, Bodey et al teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (see page 2668, column 2, in particular). In the absence of in vivo data, it is unpredictable which disease would be treated by the claimed pharmaceutical composition or the claimed method. Further, treating any diseases in the absence of in vivo data is unpredictable since the antibody may have other functional properties, known or unknown, that may make the antibody unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addition, Spitler et al recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Further, the specification does not teach how to make any antibody which competitively inhibits the binding of antibody having the CDR sequence set out in claim 1 to the CD23 (FcRII) type II molecule expressed on haematopoietic cells as set forth in claims 3, 21 and 22 without the amino acid sequence or the corresponding nucleotide sequence. Until screening library has

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identified such antibody, the specification merely extends an invitation to one skilled in the art for further experimentation to arrive at the claimed invention.

With regard to claims 8 and 9, there is insufficient guidance as to the structure of the other amino acid sequence encoded by the other polynucleotide sequence in the claimed antibody which binds to the CD23 (FcRII) type II molecule that expressed on haematopoietic cells.

Since the antibodies mentioned above are not enabled, it follows that any pharmaceutical composition comprising said antibody in combination with any immunomodulatory or anti-inflammatory agent and/or acceptable excipient are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In *re wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/27/04 have been fully considered but are not found persuasive.

Applicants' position is that Claims 1 and 8-9 have been amended to clarify that the antibody binds to CD23. Claims 3 and 21-22 are directed to antibody that competitively inhibits (i.e., inhibitory antibodies) the binding of an antibody which binds to CD23. Claim 20 is directed to a method of selecting inhibitory antibodies. Given CD23-specific antibodies, methods for generating anti-CD23 antibodies and inhibitory antibodies, and binding assays which are disclosed by Applicants in their specification, it would not require undue experimentation to generate the antibodies of claims 3 and 21-22. CD23 antigen would be used to identify other CD23-specific antibodies (i.e., candidate inhibitory antibodies), these other CD23-specific antibodies would be added to a binding assay with C11 antibody (or any of the variant antibodies based on the amino acid sequences of C11 CDRs), and those which competitively inhibited binding between C11 and CD23 would be selected as inhibitory antibodies. In particular, a person of skill in the art has no need a priori to know the structure or amino acid sequences of CDRS of such inhibitory antibodies. The skilled artisan would simply screen a library of antibodies for one

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that "competitively inhibits" binding to CD23. In no way can such a procedure be considered an undue burden. The claimed inhibitory antibodies are defined by a combination of structural and functional characteristics. As noted above, the amino acids at each of the positions recited in claims 6-7 are clear by reference to Figs. 1-2. These amino acids are not "undisclosed" as alleged on page 7 of the Action because a unique amino acid is found at each position of the C11 antibody. Claims 12 and 18-19 are directed to treatment or prophylaxis using an anti-CD23 antibody. The disorders listed in claim 12 are related to inflammation and other immune system defects. This is consistent with the art-known role of CD23 in such disorders, see the art already of record at page 4, line 55, et seq. of EP 0788513 and column 38, line 43, et seq. of U.S. Patent 6,011,138. In particular, CD23 is implicated in arthritis, see Plater-zyberk et al. (Nat. Med. 1:781-785, 1995) which is already of record and subsequently confirmed by Kleinau et al. (J. Immunol. 162:4266-4270, 1999) which is submitted herewith. The Action provides no evidence or reasoning which is inconsistent with the teaching on page 14 of Applicants' specification that the specific anti-CD23 anti-bodies claimed here would be useful in the treatment or prophylaxis of the disorders listed in claim 12. Antibodies of the claimed invention can be used to block the function of cell surface or soluble CD23 (e.g., mediation of cell adhesion, regulation of IgE and histamine release, rescue of B cells from apoptosis and regulation of myeloid growth) such that the disorders recited in claim 12 are treated or prevented. Other methods of blocking CD23 function are taught on page 13, lines 10-22, of Applicants' specification. As noted in Applicants' previous response, Section 112 and case law do not require in vivo working examples to enable these claims because it would not require undue experimentation to show that an anti-CD23 antibody is effective in treatment or prophylaxis. No fact or law was cited in the Action to contradict Applicants' teaching. Therefore, if this rejection is maintained, the Patent Office is requested to provide evidence as required by Marzocchitnat anti-CD23 antibody would not have therapeutic or prophylactic effect when administered to patients afflicted with the recited disorders. Abaza et al., Ngo et al., and Kuby et al. are not relevant to Applicants' claims because the amino acid sequences recited in those claims are specific and they have been shown to be involved in binding of CD23 or antibody function. Van Noort et al. is concerned with induction of disease by various antigens', it discloses nothing relevant to the effectiveness of anti-CD23 antibody in treating or preventing disease. A working example is not required when no evidence has been presented to contradict Applicants' teaching that the anti-CD23 antibodies claimed here can be used in treatment or prophylaxis of the listed disorders. Couzin, Bodey et al., and Spittler

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et al. also disclosed nothing relevant to use of anti-CD23 antibody in treatment or prophylaxis. The latter two references' discussion of cancer vaccines disregards the success of several antibodies in treating cancer. No evidence was presented that anti-CD23 antibodies would not be effective in treatment or prophylaxis of the disorders listed in claim 12.

In contrast to applicant's assertion that the claimed specific anti-CD23 anti-bodies would be useful in the treatment or prophylaxis of the disorders listed in claim 12 and the office action does not provide sufficient evidence to the contrary, The specification discloses only one monoclonal antibody that binds to CD23 (FC ϵ RII), a type II molecule expressed on haematopoietic cells wherein the antibody comprises the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 1 and SEQ ID NO: 2 for detection of disorder such as the ones recited in claim 12. The specification discloses only one humanized antibody that binds to CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 17 and SEQ ID NO: 18. The specification further discloses the monoclonal CD23 antibody that binds to the CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13. The specification further discloses that the said monoclonal antibody has affinity constant (K_a) approximately 9×10^{10} /mol for screening for competitive inhibitor. The specification merely lists the antibodies of the present invention are believed to be useful in the treatment or prophylaxis of diseases such as the ones recited in claim 12 (page 14).

However, the specification does not teach how to make all antibody as set forth in claims 1-10, 12, and 18-22 having any heavy and light chain framework, any murine residues at position 49, 66, 76, 77 and 94 in the heavy chain, any murine residues at position 64 in the light chain without the amino acid sequence, much less about how to treat or prophylaxis of any disorder such as lupus erythematosus, Hashimotos thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel

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disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema, GVH, COPA, insulinitis, bronchitis (particularly chronic bronchitis), diabetes (particularly Type 1 diabetes) and B-cell malignancies.

As evident by Ward et al who teaches that the use of rodent monoclonal antibodies in therapy is limited by the immunogenicity of rodent of these proteins in xenogeneic hosts (See page 79, col. 1, in particular) and short half-life (page 87, col. 1, in particular). Ward et al teach chimeric antibodies still contain rodent framework which result in the generation of anti-mouse variable domain response while humanized antibodies still contain rodent hypervariable regions grafted to human framework sequences (See page 79, col. 2, pars 1-2, in particular). Ward et al further teach changing some of the amino acids in the effector domain or the Fc region of the antibody molecules can lead to either increase or decrease the targeted effector function, leading to increase or decrease its half-life, or abolish its complement mediated lysis (See entire document). Given the chronic nature of the disorders such as arthritis, lupus erythematosus, Hashimotos thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema and the long term treatment using the antibody, it is not clear the reliance of antibody such as monoclonal antibody is effective for treating chronic autoimmune diseases in the absence of in vivo working example.

Mavromatis et al teach agent such as monoclonal antibodies when use individually are unlikely to lead to a significant prolongation of patient survival in the treatment of chronic lymphocytic leukemia (See page 1879, col. 2, in particular).

Autoimmune diseases such as the ones recited in claim 12 can be species- and model-dependent. It is not clear that the reliance on in vitro binding assays accurately reflects the relative efficacy of using any undisclosed antibody for the claimed therapeutic strategy.

Van Noort *et al* teach that induction of EAE with MBP does not result in the development of relapse and the clinical course may be different than that after treatment with other antigen such as SCH and PLP (See page 170, in particular). Further, there is no showing of treating any animal with the claimed antibody alone or in combination with any immunomodulatory or anti-inflammatory agent in the specification as filed demonstrating the claimed pharmaceutical composition and method is effective for treating or preventing a wide range of diseases from autoimmune disease to B cell malignancy.

Further, it is not clear the use of antibody that binds to CD23 (FcRII) type II molecule expressed on haematopoietic cells is effective to treat disorder such as the ones recited in claim 12 that is associated with an increase in *soluble* CD23. With regard to autoimmune disease, Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document, Science 300: 1862-65, 2003).

With regard to B cell malignancies, Bodey *et al* teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (see page 2668, column 2, in particular). In the absence of *in vivo* data, it is unpredictable which disease would be treated by the claimed pharmaceutical composition or the claimed method. Further, treating any diseases in the absence of *in vivo* data is unpredictable since the antibody may have other functional properties, known or unknown, that may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addition, Spitler *et al* recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Further, the specification does not teach how to make any antibody which competitively inhibits the binding of antibody having the CDR sequence set out in claim 1 to the CD23 (FcRII) type II molecule expressed on haematopoietic cells as set forth in claims 3, 21 and 22 without the amino acid sequence. Until such antibody has been identified, the specification merely extends an invitation to one skilled in the art for further experimentation to arrive at the scope of the claimed invention.

With regard to claims 8 and 9, there is insufficient guidance as to the structure of the other amino acid sequence encoded by the other polynucleotide sequence in the claimed antibody which binds to the CD23 (FcRII) type II molecule expressed on haematopoietic cells.

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Since the antibodies mentioned above are not enabled, it follows that any pharmaceutical composition comprising said antibody in combination with any immunomodulatory or anti-inflammatory agent and/or acceptable excipient are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

7. Claims 1-10, 12, and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) all antibody which is comprised of the amino acid sequence without the heavy and light chain framework regions as set forth in claims 1-2, (2) all antibody which competitively inhibits the binding of the any antibody having the CDR sequence as set forth in claims 3, 21 and 22, (3) all antibody which comprises the amino acid sequence as set forth in claim 6 in which the framework of the heavy chain "includes" all amino acid residues from the murine antibody at any positions 49, 66, 76, 77 and 94 by the Kabat numbering system, (4) all antibody which comprises the amino acid sequence as set forth in claim 7 in which the framework of the light chain "includes" all amino acid residues from the murine antibody at any position 64 by the Kabat numbering system, (5) a method of treatment or prophylaxis of any disorder such as lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephritic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, rhinitis, eczema, GVH, COPA, insulinitis, bronchitis (particularly chronic bronchitis), diabetes (particularly Type 1 diabetes) and B-cell malignancies using all antibody which is comprised of the amino acid sequence *without* the heavy and light chain framework regions as set forth in claims 1, and (6) any pharmaceutical formulation comprising any antibody mentioned above and a pharmaceutically acceptable excipient.

The specification discloses only one monoclonal antibody that binds to CD23 (FCεRII), a type II molecule expressed on haematopoietic cells wherein the antibody comprises the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 1 and SEQ ID NO: 2 for detection of disorder such as the ones recited in claim 12. The specification discloses

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only one humanized antibody that binds to CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising the amino acid sequences encoded by the nucleotide sequences according to SEQ ID NO: 17 and SEQ ID NO: 18. The specification further discloses the monoclonal CD23 antibody that binds to the CD23 (FC ϵ RII) type II molecule expressed on haematopoietic cells comprising light chain variable domains CDRL1, CDRL2, CDRL3, heavy chain variable domains CDRH1, CDRH2 and CDRH3 wherein CDRL1 consisting of the amino acid sequence RSSKSLLY KDGKTYLN of SEQ ID NO: 1, CDRL2 consisting of the amino acid sequence LMSTRAS of SEQ ID NO: 5, CDRL3 consisting of the amino acid sequence QQLVEYPFT of SEQ ID NO: 7, CDRH1 consisting of the amino acid sequence GYWMS of SEQ ID NO: 9, CDRH2 consisting of the amino acid sequence EIRLKSDNYATHYAESVKG of SEQ ID NO: 11 and CDRH3 consisting of the amino acid sequence FID of SEQ ID NO: 13. The specification further discloses that the said monoclonal antibody has affinity constant (K_a) approximately 9×10^{10} /mol for screening for competitive inhibitor.

With the exception of the specific monoclonal, humanized and chimeric antibodies mentioned above, there is inadequate written description about the framework of the heavy and light chain in claims 1-2 because SEQ ID NO: 3, 5, 7, 9, 11 and 13 are merely fragments of the variable regions of the antibody. Further, there is inadequate written description about the amino acid residues at the cited positions from which murine antibody to be included in the framework of the heavy chain (claim 6) and the light chain (claim 7). There is inadequate written description about the *amino acid residues at position 64* of the light chain to be “included” from which antibody without the amino acid sequence. Likewise, there is inadequate written description about the amino acid residues to be “included” in addition to which undisclosed framework of the heavy and light chain in claim 1 without the amino acid sequence. Claim 3 encompasses all antibodies which competitively inhibit the binding of an antibody having the CDR sequences set out in claim 1. However, the specification discloses only one monoclonal antibody, and one humanized or chimeric antibody that bind to CD23. There is inadequate written description about the structure of any antibody which competitively inhibits the binding of an antibody having the CDR sequences set out in claim 1 without the amino acid sequence. With regard to claims 8, 9 and claims 21-22 dependent therefrom, there is inadequate written description about the other amino acid sequences encoded by the other nucleotide sequence because the term “or” merely requires one or the other sequence. Since the complete structure of the antibody in claim 1 is not

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adequately described, it follows that the methods and the pharmaceutical composition using the undisclosed antibody are not adequately described.

Finally, the specification discloses only three antibodies that bind to CD23, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/27/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

In response, the specific amino residues at the cited positions from mouse C11 antibody is not recited in the claims. Further, there is inadequate written description about the framework of the heavy and light chain in claims 1-2 because SEQ ID NO: 3, 5, 7, 9, 11 and 13 are merely fragments of the variable regions of a monoclonal antibody. There is inadequate written description about the amino acid residues at the cited positions from which murine antibody to be included in the framework of the heavy chain (claim 6) and the light chain (claim 7). Further, position 64 in the light chain is only *one* position. However, there are more than one amino acid residues to be included. There is inadequate written description about the amino acid residues to be included in addition to which undisclosed framework of the heavy and light chain in claim 1.

With regard to claim 3, there is inadequate written description about the structure associated with function of any antibody which competitively inhibits the binding of an antibody having the cited CDR sequences set out in claim 1 without the amino acid sequence.

With regard to claims 8, 9 and claims 21-22 dependent therefrom, there is inadequate written description about the other amino acid sequences encoded by the other nucleotide sequence because the term "or" merely requires one or the other sequence. Since the complete structure of the antibody in claim 1 is not adequately described, it follows that the methods and the pharmaceutical composition comprising the undisclosed antibody are not adequately described.

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Finally, the specification discloses only three antibodies that bind to CD23, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of “the framework of the heavy chain *includes* the amino acid residues” in claim 6 is indefinite and ambiguous because the specific amino acid residues at position 49, 66, 76, 77 and 94 are not recited in the claim. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. It is suggested that the claim be amended to recite “The antibody according to claim 1 wherein the framework of the heavy chain *retains* the mouse heavy chain amino acid residues at position 49, 66, 76, 77 and 94 according to Figure 1”.

Likewise, the “amino acid residues from the murine antibody at position 64” is ambiguous and indefinite because the specific amino acid residue from the framework of the light chain of which murine antibody is not recited in the claim. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. It is suggested that the claim be amended to recite “The antibody according to claim 1 wherein the framework of the light chain retains the mouse light chain amino acid residue at position 64 according to Figure 2”.

Applicants’ arguments filed 7/27/04 have been fully considered but are not found persuasive.

Applicants’ position is that the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

In response, the specific amino residues at the cited positions from mouse C11 antibody is not recited in the claims.

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10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 3, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Wakai et al (Hybridoma 12(1): 25-43, Feb 1993; PTO 892).


Wakai *et al* teach various antibodies that bind to CD23 (FcRII) expressed on the cell surface. The reference antibodies appear to be same antibody which competitively inhibits the binding of an antibody having the CDR sequence set out in claim 1 that binds to CD23 molecule expressed on haematopoietic cells (See entire document, abstract, in particular). Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

12. No claim is allowed.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.
14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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